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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,915	03/23/2004	Frances Louisa Titus	48170.0004OPC832	4427

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Medtronic
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EXAMINER	
JOIKE, MICHELE K	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
07/14/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,915	TITUS ET AL.	
	Examiner	Art Unit	
	MICHELE K. JOIKE	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *1-6,16-20,31-35 and 41-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-15, 21-30, 36-40 and 44-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed April 22, 2009. Claims 1-49 are pending in the application. Claims 1-6, 16-20, 31-35 and 41-43 are pending in the application are withdrawn from consideration for being directed non-elected subject matter. Claims 7-15, 21-30, 36-40 and 44-49 are currently under examination.

Any rejection of record in the previous Office Action, mailed December 1, 2008 that is not addressed in this action has been withdrawn. Because this Office Action introduces new rejections other than those set forth in the previous Office Action, and are not necessitated by amendment, this Office Action is Non-Final.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-15, 21-30, 36-40 and 44-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear to what LMP-1s is referring. While it appears that LMP-1s is a shortened LMP-1, and the specification teaches that it can be SEQ ID NO:s 1-8, it is unclear if LMP-1s is limited to one of these SEQ Ids, or can be any LMP-1 that is shortened, even by one amino acid.

Response to Arguments Pertaining to 35 USC 103(a)

Applicants assert that the references do not teach which regions of the proteins taught are osteoinductive regions. However, LMP-1s disclosed by Hair et al. is a truncated version of LMP-1 that has been demonstrated with osteoinductive activity. As such, it meets the limitation of an isolated osteoinductive region of an LMP-1 protein.

Applicants also assert that the amended claims are drawn to a method of inducing bone formation in a mammal by administering an effective amount of a fusion polypeptide that comprises a protein transduction domain and isolated osteoinductive region of an LMP-1 protein, which has less than 100% sequence homology with LMP-1, and none of the references disclose this limitation.

This argument is considered persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of 35 USC 103(a).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7-9, 12-15, 36-38, 44 and 48 are rejected under 35 U.S.C. 103(a) as being obvious over Hair et al (US 6,521,750) or (US 6,858,431) in view of Nagahara et al and in further view of Liu et al.

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Hair et al. teach ex vivo transfection of bone marrow cells, osteogenic precursor cells or mesenchymal stem cells with nucleic acid that encodes LMP or HLMP, followed by reimplantation of the transfected cells in the donor for treating bone-related disorder and inducing new bone formation (see col.4 5th paragraph). Hair et al. also teach introducing expression vector encoding human LMP1 into rat calvarial cells induces bone nodule formation and mineralization (see col. 19 bottom paragraph through col.20 top paragraph). Hair et al. further teach that expression of LMP in bone progenitor cells induces differentiation (see col.20 bottom paragraph through col.21 4th paragraph). Hair et al. also demonstrate that a fusion of HIS tagged human LMP-1 also induces bone nodule formation (see col. 22, 1st paragraph).

However, Hair et al. do not teach a method of inducing bone formation in a mammal or inducing osteoblast differentiation in a progenitor cell comprising administering an effective amount of a fusion polypeptide comprising a protein transduction domain and at least one osteoinductive polypeptide, or an osteoinductive polypeptide that has less than 100% homology to LMP-1, RLMP and LMP-1s.

Nagahara et al. teach a method of transducing full length TAT fusion proteins into mammalian cells. Nagahara et al. demonstrate that TAT-p27 induces cell migration in hepatocytes transduced with this fusion protein (see page 1451, 1st col., 2nd paragraph). Nagahara et al. further teach that TAT fusion proteins may be transduced into a variety of cell types including bone marrow stem cells, osteoclasts, osteosarcoma etc (see page 1450, 1st col.) Nagahara et al. also teach different fusion proteins of TAT which are capable of induce biological response in vivo (see page 1451, Table 1).

However, Nagahara et al. do not teach a method of inducing bone formation, wherein an osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP and LMP-1s.

Liu et al (J. of Bone and Mineral Res. 17(3): 406-414, 2002, especially p. 406) teach a truncated version of hLMP-1, LMP-1(t). LMP-1(t) would have a different amino acid sequence from LMP-1, since it is full length, and RLMP, since the peptide is rat and not human, and absent evidence to the contrary is different from LMP-1s, because as noted above, there is no indication what the peptide sequence is for LMP-1s, and the specification of the instant application teaches that it can be SEQ ID NO:s 1-8, which are much shorter that the 223 amino acids of LMP-1(t).

It would have been obvious to one of ordinary skill in the art to make TAT-LIM fusion proteins to induce bone formation and progenitor cell differentiation, wherein the osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP and LMP-1s, based on the combined teaching of Hair et al., Nagahara et al and Liu et al. One of ordinary skill in the art would be motivated to do so because cellular manipulation by transfection or viral introduction of cDNA expression vectors presents various difficulties including massive overexpression, broad cell to cell intracellular concentration rages of expressed protein and low percentage of cells targeted (see Nagahara et al., page 1449, 1st col., 1st paragraph). Since Hair already demonstrate that LMP can induce bone formation and differentiation, an ordinary artisan would attach TAT to LMP so that LMP may cross cell membrane and reach target cells and alleviate the problem with gene therapy. One would be motivated to use osteoinductive polypeptide has less than

100% homology to LMP-1, RLMP and LMP-1s, because Liu et al teaches that LMP-1(t) has identical effects as the full-length protein. The level of skill in the art is high as demonstrated by Nagahara, TAT fusion proteins may be transducted to a variety of cell types. An ordinary would have reasonable expectation of success to attach TAT to LMP and administering it in an effective amount to induce bone formation and differentiation in a mammal. Furthermore, using hydrogel to load the fusion protein is routine practice to protect the protein from degradation. Making the fusion protein and achieving predictable result would have been prima facie obvious to the ordinary artisan at the time the invention was made.

Claims 7-9, 12-15, 21-23, 26-30, 36-38, 44, 46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boden et al. (Endocrinology 1998, vol. 139, no.12, pages 5125-5134), in view of Nagahara et al. and van Beuningen et al. (Osteoarthritis and Cartilage, 1998. Vol.6, pages 306-317), and in further view of Liu et al.

Boden et al. teach ex vivo transfection of bone marrow cells, osteogenic precursor cells or msenchymal stem cells with nucleic acid that encodes LMP or HLMP, followed by reimplantation of the transfected cells in the donor for treating bone-related disorder and inducing new bone formation (page 5133, Figure 9). Boden et al. also teach introducing expression vector encoding human LMP1 into rat calvarial cells induces bone nodule formation and mineralization. Boden et al. further teach that expression of LMP in bone progenitor cells induces differentiation (see page 5131,

Figure 6). Boden et al. also demonstrate that LMP induces genes such as BMP-2 expression and thus is an important regulator for osteoblast differentiation (see page 5132, 2nd col., 1st paragraph).

However, Boden et al. do not teach a method of inducing bone formation in a mammal or inducing osteoblast differentiation in a progenitor cell comprising administering an effective amount of a fusion polypeptide comprising a protein transduction domain and at least one osteoinductive polypeptide. Boden et al. do not each LMP induces proteoglycan production in a mammal, or an osteoinductive polypeptide that has less than 100% homology to LMP-1, RLMP and LMP-1s..

Nagahara et al. teach a method of transducing full length TAT fusion proteins into mammalian cells. Nagahara et al. demonstrate that TAT-p27 induces cell migration in hepatocytes transduced with this fusion protein (see page 1451, 1st col., 2nd paragraph). Nagahara et al. further teach that TAT fusion proteins may be transduced into a variety of cell types including bone marrow stem cells, osteoclasts, osteosarcoma etc (see page 1450, 1st col.) Nagahara et al. also teach different fusion proteins of TAT which are capable of induce biological response in vivo (see page 1451, Table 1).

van Beuningen et al. teach that the synthesis of proteoglycan including aggrecan is increased following BMP-2 injection to the knee of a rat model (see page 309, 2nd col., 1st paragraph).

Liu et al (J. of Bone and Mineral Res. 17(3): 406-414, 2002, especially p. 406) teach a truncated version of hLMP-1, LMP-1(t). LMP-1(t) would have a different amino acid sequence from LMP-1, since it is full length, and RLMP, since the peptide is rat and

not human, and absent evidence to the contrary is different from LMP-1s, because as noted above, there is no indication what the peptide sequence is for LMP-1s, and the specification of the instant application teaches that it can be SEQ ID NO:s 1-8, which are much shorter that the 223 amino acids of LMP-1(t).

It would have been obvious to one of ordinary skill in the art to one of ordinary skill in the art to make TAT-LIM fusion proteins to induce bone formation and progenitor cell differentiation, wherein the osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP and LMP-1s, based on the combined teaching of Boden et al., Nagahara et al and Liu et al. One of ordinary skill in the art would be motivated to do so because cellular manipulation by transfection or viral introduction of cDNA expression vectors presents various difficulties including massive overexpression, broad cell to cell intracellular concentration rages of expressed protein and low percentage of cells targeted (see Nagahara et al., page 1449, 1st col., 1st paragraph). Since Boden already demonstrate that LMP can induce bone formation and differentiation, an ordinary artisan would attach TAT to LMP so that LMP may cross cell membrane and reach target cells and alleviate the problem with gene therapy. The level of skill in the art is high as demonstrated by Nagahara, TAT fusion proteins may be transducted to a variety of cell types. An ordinary would have reasonable expectation of success to attach TAT to LMP and administering it in an effective amount to induce bone formation and differentiation in a mammal. One would be motivated to use osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP and LMP-1s, because Liu et al teaches that LMP-1(t) has identical effects as the full-length protein. Furthermore,

using hydrogel to load the fusion protein is routine practice to protect the protein from degradation. Moreover, since Boden demonstrates that BMP-2 is increased up to 38 fold at protein level following LMP expression, and van Beuningen et al. have shown that proteoglycan level is increased following BMP-2 injection in an animal model, it would have been reasonable for an ordinary artisan to expect that following administration of TAT LMP to a mammal, the proteoglycan synthesis will be induced. Making the fusion protein and achieving predictable result would have been prima facie obvious to the ordinary artisan at the time the invention was made.

Response to Arguments Pertaining to Double Patenting

Applicants assert that the references do not teach which regions of the proteins taught are osteoinductive regions. However, LMP-1s disclosed by Hair et al. is a truncated version of LMP-1 that has been demonstrated with osteoinductive activity. As such, it meets the limitation of an isolated osteoinductive region of an LMP-1 protein.

Applicants also assert that the amended claims are drawn to a method of inducing bone formation in a mammal by administering an effective amount of a fusion polypeptide that comprises a protein transduction domain and isolated osteoinductive region of an LMP-1 protein, which has less than 100% sequence homology with LMP-1, and none of the references disclose this limitation.

This argument is considered persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made.

Additionally, a new double patenting rejection is added below over claims 1 and 10 of US 7,504,374.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7-9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,858,431, in view of Nagahara et al, and in further view of Liu et al.

Hair et al. teach ex vivo transfection of bone marrow cells, osteogenic precursor cells or mesenchymal stem cells with nucleic acid that encodes LMP or HLMP, followed by reimplantation of the transfected cells in the donor for treating bone-related disorder and inducing new bone formation (see col.4 5th paragraph). Hair et al. also teach

introducing expression vector encoding human LMP1 into rat calvarial cells induces bone nodule formation and mineralization (see col. 19 bottom paragraph through col.20 top paragraph). Hair et al. further teach that expression of LMP in bone progenitor cells induces differentiation (see col.20 bottom paragraph through col.21 4th paragraph). Hair et al. also demonstrate that a fusion of HIS tagged human LMP-1 also induces bone nodule formation (see col. 22, 1st paragraph).

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However, Nagahara et al. do not teach a method of inducing bone formation, wherein an osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP and LMP-1s.

Liu et al (J. of Bone and Mineral Res. 17(3): 406-414, 2002, especially p. 406) teach a truncated version of hLMP-1, LMP-1(t). LMP-1(t) would have a different amino acid sequence from LMP-1, since it is full length, and RLMP, since the peptide is rat and not human, and absent evidence to the contrary is different from LMP-1s, because as noted above, there is no indication what the peptide sequence is for LMP-1s, and the specification of the instant application teaches that it can be SEQ ID NO:s 1-8, which are much shorter that the 223 amino acids of LMP-1(t).

It would have been obvious to one of ordinary skill in the art to make TAT-LIM fusion proteins to induce bone formation and progenitor cell differentiation, wherein the osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP and LMP-1s, based on the combined teaching of Hair et al., Nagahara et al and Liu et al. One of ordinary skill in the art would be motivated to do so because cellular manipulation by transfection or viral introduction of cDNA expression vectors presents various difficulties including massive overexpression, broad cell to cell intracellular concentration rages of expressed protein and low percentage of cells targeted (see Nagahara et al., page 1449, 1st col., 1st paragraph). Since Hair already demonstrate that LMP can induce bone formation and differentiation, an ordinary artisan would attach TAT to LMP so that LMP may cross cell membrane and reach target cells and alleviate the problem with gene therapy. One would be motivated to use osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP and LMP-1s, because Liu et al teaches that LMP-1(t) has identical effects as the full-length protein. The level of skill in the art is high as demonstrated by Nagahara, TAT fusion proteins may be transducted to a variety of cell

types. An ordinary would have reasonable expectation of success to attach TAT to LMP and administering it in an effective amount to induce bone formation and differentiation in a mammal. Furthermore, using hydrogel to load the fusion protein is routine practice to protect the protein from degradation. Making the fusion protein and achieving predictable result would have been prima facie obvious to the ordinary artisan at the time the invention was made.

Claims 7-9, 36-38 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,521,750, in view of Nagahara et al, and I n further view of Liu.

Boden et al. teach ex vivo transfection of bone marrow cells, osteogenic precursor cells or msenchymal stem cells with nucleic acid that encodes LMP or HLMP, followed by reimplantation of the transfected cells in the donor for treating bone-related disorder and inducing new bone formation (page 5133, Figure 9). Boden et al. also teach introducing expression vector encoding human LMP1 into rat calvarial cells induces bone nodule formation and mineralization. Boden et al. further teach that expression of LMP in bone progenitor cells induces differentiation (see page 5131, Figure 6). Boden et al. also demonstrate that LMP induces genes such as BMP-2 expression and thus is an important regulator for osteoblast differentiation (see page 5132, 2nd col., 1st paragraph).

However, Boden et al. do not teach a method of inducing bone formation in a mammal or inducing osteoblast differentiation in a progenitor cell comprising

administering an effective amount of a fusion polypeptide comprising a protein transduction domain and at least one osteoinductive polypeptide. Boden et al. do not each LMP induces proteoglycan production in a mammal, or an osteoinductive polypeptide that has less than 100% homology to LMP-1, RLMP and LMP-1s..

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Liu et al (J. of Bone and Mineral Res. 17(3): 406-414, 2002, especially p. 406) teach a truncated version of hLMP-1, LMP-1(t). LMP-1(t) would have a different amino acid sequence from LMP-1, since it is full length, and RLMP, since the peptide is rat and not human, and absent evidence to the contrary is different from LMP-1s, because as noted above, there is no indication what the peptide sequence is for LMP-1s, and the specification of the instant application teaches that it can be SEQ ID NO:s 1-8, which are much shorter that the 223 amino acids of LMP-1(t).

It would have been obvious to one of ordinary skill in the art to one of ordinary skill in the art to make TAT-LIM fusion proteins to induce bone formation and progenitor cell differentiation, wherein the osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP and LMP-1s, based on the combined teaching of Boden et al., Nagahara et al and Liu et al. One of ordinary skill in the art would be motivated to do so because cellular manipulation by transfection or viral introduction of cDNA expression vectors presents various difficulties including massive overexpression, broad cell to cell intracellular concentration rages of expressed protein and low percentage of cells targeted (see Nagahara et al., page 1449, 1st col., 1st paragraph). Since Boden already demonstrate that LMP can induce bone formation and differentiation, an ordinary artisan would attach TAT to LMP so that LMP may cross cell membrane and reach target cells and alleviate the problem with gene therapy. The level of skill in the art is high as demonstrated by Nagahara, TAT fusion proteins may be transducted to a variety of cell types. An ordinary would have reasonable expectation of success to attach TAT to LMP and administering it in an effective amount to induce bone formation and differentiation in a mammal. One would be motivated to use osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP and LMP-1s, because Liu et al teaches that LMP-1(t) has identical effects as the full-length protein. Furthermore, using hydrogel to load the fusion protein is routine practice to protect the protein from degradation. Moreover, since Boden demonstrates that BMP-2 is increased up to 38 fold at protein level following LMP expression, and van Beuningen et al. have shown that proteoglycan level is increased following BMP-2 injection in an animal model, it

would have been reasonable for an ordinary artisan to expect that following administration of TAT LMP to a mammal, the proteoglycan synthesis will be induced. Making the fusion protein and achieving predictable result would have been prima facie obvious to the ordinary artisan at the time the invention was made.

Claims 7-9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 10 of U.S. Patent No. 7,504,374. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and US 7,504,374 teach a method for inducing bone formation, wherein: a) an LMP-1 protein or a fragment thereof that induces bone formation with a PTD attached is administered to a targeted site of said subject in amounts effective to induce deposition and maturation of bone.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-15, 21-30 and 36-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. This rejection is maintained for reasons of record. New claims 44-49 are added to the rejection.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. Claims 7, 21 and 36 recite at least one isolated osteoinductive region of an LMP-1 protein, wherein the osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP and LMP-1s. The specification discloses peptides derived from LMP-1 and LMP-3 that comprises a forty amino acid sequence and its overlapping region have osteoinductive potential as indicted in Figure 6. Figure 6 outlines peptide 1-8 has bone growth activity

ranging from moderate to excellent bone growth. However, the specification fails to disclose which part of the LMP-1 or LMP-3 SEQ ID NO:1-8 is located. According to the disclosure of the specification, the fragment 94-133 of amino acid sequence of human LMP-1, which is common to LMP-1 and LMP-3 has osteoinductive activity. However, SEQ ID NO:1-4 and 7-8 are shorter than 40 amino acid in length. Furthermore, the specification teaches that "[a] variant amino acid molecule of the present invention, therefore, has less than one hundred percent, but at least about fifty percent, and preferably at least about eighty to about ninety percent amino acid sequence homology or identity to the amino acid sequence of a polypeptide comprising the amino acid sequence of LMP-1, LMP-2, LMP-3, SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, or a polypeptide as in SEQ ID NO 8." The claims do not limit the homology to at least 50%, but even if they did a representative number of species have not been sufficiently described by other relevant identifying characteristics. The specification also fails to disclose whether these peptides have proteoglycan producing activity or can induce osteoblast differentiation. What's known in the prior art is not sufficient to make up the deficiency of the specification. Boden et al. teach ex vivo transfection of bone marrow cells, osteogenic precursor cells or msenchymal stem cells with nucleic acid that encodes LMP or HLMP, followed by reimplantation of the transfected cells in the donor for treating bone-related disorder and inducing new bone formation (page 5133, Figure 9). Boden et al. also teach introducing expression vector encoding human LMP1 into rat calvarial cells induces bone nodule formation and mineralization. Boden et al. further teach that

expression of LMP in bone progenitor cells induces differentiation (see page 5131, Figure 6). Boden et al. also demonstrate that LMP induces genes such as BMP-2 expression and thus is an important regulator for osteoblast differentiation (see page 5132, 2nd col., 1st paragraph). However, Boden does not provide any information with regard to parts of the LMP-1 or LMP-3 that has osteoinductive activity including bone growth, osteoblast differentiation and proteoglycan production. According to the disclosure of the specification, a skilled artisan cannot envision which region of the human LMP-1 or LMP-3 or LMP-1 or 3 from other species would have osteoinductive activity including bone growth, osteoblast differentiation and proteoglycan production. The specification discloses only 8 peptides that has bone growth activity and fails to disclose what common structure theses peptides share. The claimed genus of isolated osteoinductive region of an LMP-1, wherein the osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP and LMP-1s is broad because it comprises potentially a large number of fragments of varying length from LMP-1 from any species which may or may not have osteoinductive activity. Since the specification does not provide adequate description of the structural and functional relationship of the region that comprises such activity, it fails to demonstrate that the inventors have possession of the invention at the time the invention was filed.

Response to Arguments

Applicant's arguments filed April 22, 2009 have been fully considered but they are not persuasive.

The following grounds of traversal are presented:

Claims 7, 21 and 36 were amended to recite that the osteoinductive polypeptide comprises at least a portion of SEQ ID NO: 5. The amino acid sequences for LMP-1, LMP-2, LMP-3, RLMP and LMP-1s have been disclosed in the prior art, and a person with ordinary skill in the art has sufficient guidance to identify amino acid sequences with osteoinductive potential. One of with ordinary skill in the art would have understood from the instant disclosure that administering of the claimed peptides to a cell would induce proteoglycan synthesis and osteoblast differentiation. Fig. 6. shows that peptides disclosed in the instant specification induce bone growth. A person having ordinary skill in the art would have reasonably inferred that the osteogenic effect of these peptides is likely due, at least in part, to these peptides' ability to induce BMP synthesis because BMP's is known to play an important role in bone formation and growth. It is also well know that BMP increases proteoglycan production as well as induces osteoblast differentiation. Therefore, the person of ordinary skill in the art would have concluded that the peptides that induce bone formation (e.g., peptides with osteoiductive functionality) would also induce proteoglycan synthesis and osteoblast differentiation.

Applicant's arguments have not been found persuasive for the following reasons.

The claims have not been limited to SEQ ID NO: 5. Also, as argued above, one of with ordinary skill in the art would not have understood from the instant disclosure that administering of the claimed peptides to a cell would induce proteoglycan synthesis

and osteoblast differentiation or have osteoinductive potential, because the osteoinductive polypeptide can be less than 100% homologous to LMP-1, RLMP and LMP-1s. The specification does not provide adequate description of the structural and functional relationship of the region that comprises such activity.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELE K. JOIKE whose telephone number is (571)272-5915. The examiner can normally be reached on M-F, 10:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Michele K. Joike/
Examiner, Art Unit 1636

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